Original Article

Cessation of Vascular Endothelial Growth Factor–Targeted Therapy in Patients With Metastatic Renal Cell Carcinoma

Feasibility and Clinical Outcome

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BACKGROUND: The current treatment of metastatic renal cell carcinoma (mRCC) with vascular endothelial growth factor (VEGF)-targeted agents is continuous therapy until progression of disease (PD) or unacceptable toxicity. Chronic mild to moderate toxicity and risk of long-term toxicity ensue for some patients. It is hypothesized that patients with an initial response to treatment can maintain disease control off all therapy for a period of time. **METHODS:** A retrospective study of patients with mRCC who initiated VEGF-targeted therapy between January 2004 and December 2009 at The Cleveland Clinic Foundation, Cleveland, Ohio, or Institut Gustave-Roussy, Villejuif, France, was conducted. Patients had achieved RECIST (Response Evaluation Criteria in Solid Tumors)-defined stable disease or better on therapy, and were then taken off all therapy for reasons not including disease progression. Patient, disease, and therapy characteristics were recorded. The primary objective was progression-free survival (PFS), measured as the time from discontinuation of therapy to RECIST-defined PD. **RESULTS:** Forty patients were identified. After a median follow-up of 29.7 months (range, 4.2 to 84.7 months), 25 patients (63%) had PD off therapy (median PFS, 10.0 months; range, 1.4-27.2 months). Among these patients, 8 (32%) had progression in sites that were not previously involved with disease. Heng risk group (hazard ratio, 2.49; 95% confidence interval, 1.19-5.22; $P=.011$) and achievement of a complete response prior to discontinuing therapy (hazard ratio, 0.20; 95% confidence interval, 0.04-0.86; $P=.025$) were independent predictors of PFS in a multivariable Cox proportional hazards model. **CONCLUSIONS:** A select subset of mRCC patients achieving stable disease or better on VEGF-targeted therapy can be observed off all therapy. Further prospective investigation is warranted. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

KEYWORDS: renal cell carcinoma, vascular endothelial growth factor, sunitinib, observation, expectant management.

Current practice in the treatment of metastatic renal cell carcinoma (mRCC) with vascular endothelial growth factor (VEGF)-targeted agents is continuous treatment until progression of disease (PD) or unacceptable toxicity.[1] VEGF-targeted therapy is currently employed as an empiric sequence of monotherapies, with an initial progression-free survival (PFS) of approximately 11 months and subsequent PFS of approximately 5 to 7 months[2,3] with overall survival extending beyond 2 years. These data were generated in clinical trials in which patients were treated continuously until toxicity or disease progression, and often subsequently received multiple additional therapies continuously until further progression. Despite the greatly enhanced disease control and robust objective response rates, VEGF-targeted therapy is not felt to be curative for patients with mRCC. Acute and chronic toxicity is encountered with ongoing therapy. Furthermore, a relatively high percentage of patients treated with these agents have to discontinue treatment secondary to adverse events.[1]

Given the balance of toxicity and benefit with VEGF-targeted therapy in patients with mRCC, studies have investigated discontinuation of therapy. In a group of 12 patients who achieved a complete response (CR) on sunitinib or sorafenib with or without surgical metastasectomy, the median time to progression off all therapy was 6 months.[4] In a more recent series of 64 patients who achieved a complete response on VEGF-targeted therapy, the median time until

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progression off therapy was 8.5 months.[5] On the basis of these considerations, it was hypothesized that a subset of patients with an initial response to VEGF-targeted therapy can maintain disease control off all therapy for a period of time.

MATERIALS AND METHODS

A retrospective study was conducted of patients with mRCC who initiated VEGF-targeted therapy between January 2004 and December 2009 at The Cleveland Clinic Taussig Cancer Institute (Cleveland, Ohio) or Institut Gustave-Roussy (Villejuif, France). Patients had achieved disease control on therapy, defined as Response Evaluation Criteria in Solid Tumors (RECIST) stable disease (SD), partial response (PR), or CR. Patients were then taken off all therapy for reasons other than RECIST-defined PD and started a period of expectant management. Clinical follow-up, including restaging imaging studies, were performed at the discretion of the treating physician and generally included CT scans of the chest, abdomen, and pelvis performed every 3 to 4 months. Patient, disease, and treatment characteristics were recorded. Variables of interest included current therapy (the therapy that was held at the beginning of expectant management), reason for discontinuation of therapy, sites of metastatic involvement prior to discontinuation of therapy, and Heng risk group[6] at the time of initiation of current therapy. In addition, the history of systemic treatment prior to current VEGF-targeted therapy, prior nephrectomy, tumor histology, and dates of diagnosis of metastatic disease, initiation of therapy, discontinuation of therapy, progression of disease, and most recent staging imaging were recorded. The study cut-off date was December 31, 2010.

PFS was measured as the time from discontinuation of therapy to investigator-assessed RECIST PD and was the primary objective of the study. A Cox proportional hazards ratio model was used for statistical analysis to investigate the association of variables of interest with PFS off therapy. The analysis was performed using STATA software, version 10.

RESULTS

A total of 40 patients were identified and were included in the analysis: 18 patients (45%) from the Institut Gustav-Roussy and 22 (55%) from The Cleveland Clinic. Patient characteristics were typical of an mRCC population, with a male predominance and a median age of 64 years at the time current therapy was initiated. All patients had clear cell histology, had undergone prior nephrectomy, and had a Karnofsky performance status of 80% or better. Eighteen patients (45%) were considered of favorable risk on the basis of Heng criteria,[6] 20 (50%) were intermediate risk, and 2 patients (5%) were in the unfavorable prognostic group. The most common sites of metastatic disease were lung, lymph node, and pancreas.

The populations from the 2 centers were different with respect to RECIST status at the time of discontinuation of current therapy, with significantly more patients achieving CR on VEGF-targeted therapy at The Cleveland Clinic ($P = .015$), more patients with a prior history of VEGF targeted therapy at The Cleveland Clinic ($P = .004$), and significantly more patients receiving sunitinib at The Cleveland Clinic ($P = .007$). Otherwise, there were no significant differences between the patients from each institution.

A total of 45% of patients had received no prior systemic therapy. Eight patients (20%) had a history of VEGF-targeted therapy received before the current VEGF-targeted therapy that was held for expectant management. Fifteen patients (38%) had a history of metastasectomy.

The VEGF-targeted therapy held at the beginning of the observation period included sunitinib (55%), bevacizumab (23%), and sorafenib (18%). One patient (3%) was treated with sunitinib plus bevacizumab as part of a clinical trial. The median duration of VEGF-targeted therapy was 14.6 months (range, 2.8-79 months). At the time current therapy was stopped, 6 patients (15%) had achieved a CR, 29 (73%) had achieved PR, and 5 (13%) had SD as the best objective response (Table 1).

As noted, patients discontinued the current VEGF-targeted therapy for reasons other than RECIST-defined PD (Table 2). In most cases (73%), discontinuation of therapy could be attributed to toxicity. Where precise attribution was not possible, the reason for discontinuation of therapy was considered personal preference (15%).

There were also patients in whom therapy was held for a procedure and was not restarted (10%). In 1 patient (3%), therapy was held for economic reasons (high copayment for oral medication).

Clinical Outcome During the Observation Period

After a median follow-up of 29.7 months (range, 4.2-84.7 months), 25 patients (63%) had RECIST-defined PD (median PFS, 10.0 months; range, 1.4-27.2 months) (Fig. 2). There was no evidence on radiographic imaging or clinical examination of a "flare" phenomenon (rapid

Table 1. Patient Characteristics

	No. (%)
Patient Characteristics	
Median age (range), y	63 (50-80)
Male	31 (78)
Female	9 (22)
Clear cell histology	40 (100)
Karnofsky performance status > 80%	40 (100)
Prognostic risk variables and groups	
Corrected calcium > ULN	0 (0)
Hemoglobin < LLN	10 (25)
Platelet > ULN	3 (8)
Absolute neutrophil count > ULN	2 (5)
Lactate dehydrogenase > 1.5× ULN	2 (5)
Time to treatment < 1 year	18 (45)
MSKCC risk group favorable[10]	20 (50)
MSKCC risk group intermediate	19 (48)
MSKCC risk group poor	1 (3)
Heng risk group favorable[6]	18 (45)
Heng risk group intermediate	20 (50)
Heng risk group poor	2 (5)
Prior treatment history	
No prior systemic therapy	18 (45)
Prior VEGF therapy	8 (20)
Prior immunotherapy	11 (28)
Nephrectomy	40 (100)
Metastasectomy	15 (38)
Sites of metastasis at initiation of VEGF-targeted therapy	
Bone	3 (8)
Brain	3 (8)
Lymph node	25 (63)
Liver	5 (13)
Lung	30 (75)
Other	21 (53)
VEGF-targeted therapy held	
Sunitinib	22 (55)
Bevacizumab	10 (25)
Sorafenib	8 (20)
Median duration of therapy (range), mo	14.6 (2.8-79)
Best response to VEGF-targeted therapy	
Complete response	6 (15)
Partial response	29 (73)
Stable disease	5 (13)

Abbreviations: LLN, lower limit of the normal range; MSKCC, Memorial Sloan-Kettering Cancer Center; ULN, upper limit of the normal range; VEGF, vascular endothelial growth factor.

Table 2. Reasons for Discontinuation of Current Therapy

Reason for Discontinuing Therapy	No. (%)
Diarrhea	7 (18)
Personal choice	6 (15)
Procedure	4 (10)
Mucositis	4 (10)
Proteinuria	3 (8)
Fatigue	3 (8)
Hand-foot syndrome, rash	3 (8)
Anal abscess	2 (5)
Myocardial infarction	2 (5)
Drop in ejection fraction	2 (5)
Hypertension	2 (5)
Cerebrovascular accident	2 (5)
Transient ischemic attack	1 (3)
Hemorrhoids	1 (3)
Pneumonitis	1 (3)
Nausea	1 (3)
Economic	1 (3)

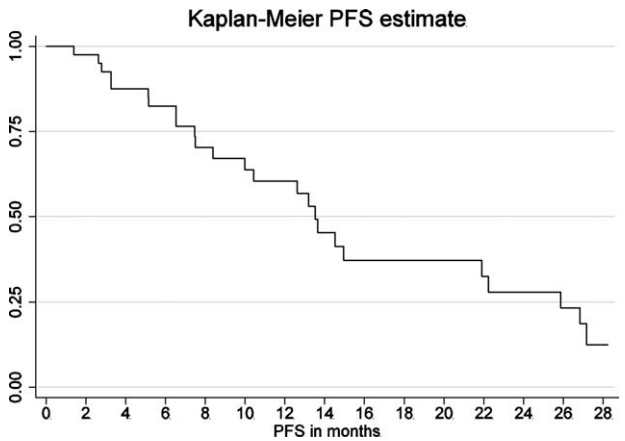

Figure 1. Kaplan-Meier estimate of progression-free survival (PFS) is shown for all patients who started a period of expectant management. Median PFS is estimated to be 13.5 months (95% confidence interval, 8.4-22.2 months).

and unexpected progression of disease after stopping targeted therapy).

Fifteen patients (37%) continued expectant management at the data cutoff date without disease progression at a median of 8.9 months (range, 4.6-28.2 months) off therapy. The overall median PFS for the entire cohort is 13.5 months (95% confidence interval [CI], 8.4-22.2 months; Fig. 1).

Of the 25 patients with disease progression off therapy, 8 patients chose to continue expectant management given the low volume and pace of disease. Seventeen patients started subsequent treatment including local therapies (surgery, radiofrequency ablation, and radiation therapy), and systemic therapies sunitinib, sorafenib, pazopanib, and everolimus. Among systemic agents, sunitinib was the most commonly used agent, with 10 patients, 7 of whom were previously on sunitinib immediately prior to the period of expectant management. Full information on response to reinitiation of systemic therapy is not available at the time of this report. All 15 patients who did not have PD are continuing the expectant management at the time of this report.

Table 3. Cox Proportional Hazard Ratios for Variables of Interest

Univariable Analysis	Hazard Ratio	*P*
Demographics		
Age (≥ 60 vs < 60)	0.96 (0.40-2.33)	.93
Sex (male vs female)	1.97 (0.81-4.78)	.13
Institution (CCF vs IGR)	0.52 (023-1.20)	.13
Follow-up data		
Duration of most recent therapy ≥ 12 mo vs < 12 mo	1.10 (0.49-2.45)	.82
Disease status at the time of initiation of VEGF inhibitor		
Presence of bone metastasis	6.26 (1.20-32.74)	**.03**
Presence of brain metastasis	1.66 (0.37-7.46)	.51
Presence of lymph node metastasis	0.65 (0.29-1.43)	.30
Presence of liver metastasis	1.01 (0.29-3.50)	.99
Presence of lung metastasis	0.52 (0.20-1.40)	.20
Presence of other metastasis	2.08 (0.88-4.93)	.10
Presence of RECIST CR at treatment stop	0.20 (0.04-0.86)	**.03**
Current treatment		
Sunitinib-based vs bevacizumab-based vs sorafenib-based	1.08 (0.65-1.78)	.77
Prior treatment history		
Prior metastasectomy	081 (0.36-1.83)	.62
Prior VEGF-targeted therapy	0.86 (0.29-2.52)	.78
Prior immunotherapy	0.97 (0.38-2.46)	.95
Heng risk variables		
MSKCC risk group (favorable/intermediate/poor)[10]	1.55 (0.84-2.86)	.16
Heng risk group (favorable/intermediate/poor)[6]	2.49 (1.19-5.22)	**.02**
Multivariable Analysis		
Heng risk group (favorable/intermediate/poor)[6]	2.24 (1.05-4.80)	**.04**
Presence of RECIST CR at treatment stop	0.19 (0.42-0.84)	**.03**

Values in bold indicate statistically significant results.
Abbreviations: CCF, Cleveland Clinic Foundation; CR, complete response; IGR, Institut Gustave Roussy; MSKCC, Memorial Sloan-Kettering Cancer Center; RECIST, Response Evaluation Criteria in Solid Tumors; VEGF, vascular endothelial growth factor.

Analysis of Factors Associated With Duration of Time Until RECIST-Defined PD Off Therapy

A univariate analysis was conducted to investigate the relationship between clinical variables and time from discontinuation of therapy until PD (Table 3). Using $P = .05$ as a cutoff, the factors that were associated with PFS were worse Heng risk group (hazard ratio [HR], 2.49; 95% CI, 1.19-5.22; $P = .02$), presence of bone metastases (HR, 6.26; 95% CI, 1.20-32.74; $P = .03$), and lack of achievement of a CR prior to discontinuing therapy (HR, 0.20; 95% CI, 0.04-0.86; $P = .03$). Using a stepwise selection algorithm with $P = .05$ as the criteria for a factor to enter and stay in the model, only more favorable Heng risk group (HR, 2.24; 95% CI, 1.05-4.80; $P = .04$) and achievement of a CR prior to discontinuing therapy (HR, 0.19; 95% CI, 0.42-0.84; $P = .03$) were independent predictors of a longer PFS off therapy.

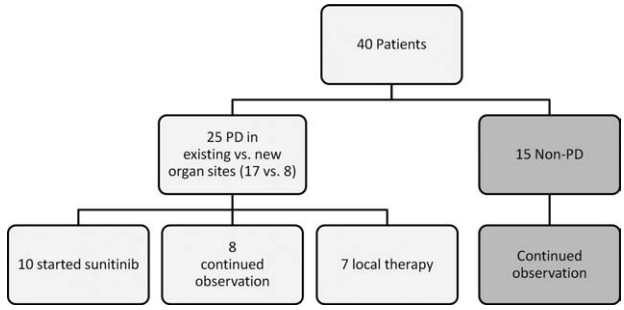

Figure 2. Diagram shows outcomes of the patients managed expectantly. PD indicates progression of disease.

DISCUSSION

This retrospective analysis demonstrates that highly select patients with mRCC can be taken off VEGF-targeted therapy and expectantly managed. After approximately 1 year receiving VEGF-targeted therapy, patients were observed on average for 10 months until RECIST-defined PD.

The patients included in this retrospective review are more inclusive than those in a similar study published recently,[5] and builds on the idea that continuous VEGF-targeted therapy may not be necessary in all patients. Instead of limiting inclusion to patients with mRCC who achieved a complete response on VEGF-targeted therapy as per previous reports, patients with RECIST-defined SD or better on VEGF-targeted therapy were included.

The reasons for holding current therapy were quite diverse. However, the majority of patients held treatment as a result of toxicity. Often, these toxicities are lower grade and chronic, which can significantly interfere with quality of life. Although these toxicities are not necessarily grade 3 toxicities that would require patients to completely discontinue therapy as in the context of a clinical trial, it is clear that lower grade chronic toxicity is a significant limitation of VEGF-targeted therapy for many patients. A strategy of periodic treatment breaks, therefore, may allow for a reduction in overall toxicity and increase in patient quality of life while maintaining overall disease control with these noncurative therapies. This hypothesis requires prospective testing. Formal quality of life assessment was not undertaken, because this was a

retrospective study, although all patients had improvement in toxicity while off treatment.

In other solid oncology disciplines, intermittent therapy, either for the most toxic drug in a given regimen or for the entire regimen, is also emerging as a potentially viable strategy. As an example, in the OPTIMOX trial, intermittent therapy with oxaliplatin while continuing 5-fluorouracil was shown to be an acceptable regimen with reduced toxicity and similar efficacy.[7] A newer study compares intermittent FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) with standard continuous FOLFIRI and finds equivalent results in overall survival and PFS after a median drug holiday of 3.5 months.[8] Furthermore, discontinuation of imatinib after 2 years of sustained complete molecular remission in patients with Philadelphia chromosome–positive chronic myelogenous leukemia resulted in a relapse-free survival of 38% at 2 years. All patients who relapsed were successfully treated into remission upon reintroduction of imatinib.[9]

It would seem intuitive that patients with more indolent disease will likely take longer to progress off therapy. However, the results of time variables representing the duration of disease (or duration of metastatic disease) measured from the time of nephrectomy (or from the time of diagnosis of metastatic disease) to the time of starting or holding current therapy were not statistically significant predictors of PFS. This may be due to the small number of patients in this analysis. However, another indicator of more indolent disease, a favorable Heng prognostic risk group, was found to be a statistically significant predictor of PFS. An observation period/intermittent approach therefore likely takes advantage of inherently indolent biology by reducing tumor burden with treatment, with inherent slow growth during the off period.

As reported, a "flare" phenomenon of disease progression, determined either radiographically or clinically, after stopping targeted therapy was not observed. However, given the retrospective nature of this analysis, precise characterization of this potential phenomenon is not possible. A clinical concern with observation in patients with mRCC would be new sites of disease in clinically relevant areas (eg, brain and bone) that could lead to significant morbidity, which might have been avoided with continuous therapy. Overall, 8 patients had new sites of disease that arose during expectant management, including 1 patient each with a new brain and bone lesion, respectively. Radiation therapy was initiated for local management of the brain and bone metastatic lesions in these patients. Notably, unlike PD identified in previously uninvolved common sites of metastatic disease, new involvement of bone and brain caused significant clinical symptoms that required immediate intervention. This is a cause for concern and is a potential limitation of expectant management. In addition, data on response to reinstituted VEGF-targeted therapy on progression of disease are incomplete, and therefore we cannot comment on its outcomes.

This study has several limitations inherent to a retrospective study, including a small sample size and an inherent selection bias, because many of these patients were managed off all therapy because the clinicians were comfortable with small volume of disease of the slow pace of disease. In addition, the frequency of imaging follow-up was at the discretion of the treating physician, which affects the reported PFS off therapy. Furthermore, there was not a matched cohort of patients who continued VEGF-targeted therapy to compare clinical outcome. This latter point is important, because treatment breaks could theoretically be associated with worse overall outcome (eg, worse overall survival), which would be critically important in a patient's and doctor's decision-making regarding the need or desire for a treatment break. Further prospective testing of this approach is therefore needed before it can be recommended.

These data generate a hypothesis that there is a select subset of patients with mRCC with disease control on VEGF-targeted therapy who can be observed off all active therapy. A more favorable prognostic risk score is associated with a longer duration of expectant management before disease progression. Whether this approach can be routinely applied to a less selective population will require prospective investigation. A phase 2 clinical trial of intermittent sunitinib is currently underway at the Cleveland Clinic (Clinicaltrials.gov identifier NCT01158222).

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No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURE

Dr. Sadeghi owns stock in Pfizer, Inc. Dr. Albiges has acted as an unpaid consultant for Pfizer, Inc and has received honoraria and research funding from Novartis. Dr. Wood has received honoraria from Pfizer, Inc; Bayer/Onyx; Genentech; and Novartis. Dr. Gilligan has received honoraria from Pfizer, Inc. Dr. Garcia has acted as a paid consultant for Pfizer, Inc; GlaxoSmithKline; and Genentech. He has also received honoraria from Pfizer, Inc; GlaxoSmithKline; and Genentech and has received research funding from Pfizer, Inc and Genentech. Dr. Dreicer has acted as a paid consultant for GTx, Boehringer, and Sanofi-Aventis and has received honoraria from Millenium Pharmaceuticals. Dr. Escudier has acted as a paid consultant for Bayer Schering Pharma; Pfizer, Inc; and Roche. He has also received honoraria from Bayer Schering Pharma; Roche; Pfizer, Inc; AVEO Pharmaceuticals; Genentech; and Novartis. Dr. Rini has

acted as a paid consultant for Onyx; Pfizer, Inc; GlaxoSmithKline; and Genentech and has received research funding from Pfizer, Inc, and GlaxoSmithKline.

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